Health and Human Services Memorandum

To: BLA File No. 97-1325

From: Judith A. Kassis, Ph.D.
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Date: April 10, 1998

Through: Philip D. Noguchi, M.D., Director, DCGT

This review is organized according to the guidance for industry document "For the submission of chemistry, manufacturing, and controls information for a therapeutic recombinant DNA-derived product or a monoclonal antibody product for *in vivo* use," August, 1996. The submission was also organized in that manner, however, many things were cross referenced and this made it very confusing to review.

Review summary:

$DAB_{389}IL-2$ is an impure product. Seragen estimates that only — of the Drug Product is active ——— The current lot release tests do not reflect this level of impurity. Although a test for ——— $DAB_{389}IL-2$ is incorporated as a lot release specification, there are no tests or specifications for ——— or ——— $DAB_{389}IL-2$ ——— Also, the test used for quantitating the ——— $DAB_{389}IL-2$ has not been adequately validated. Thus, the lot release tests do not give assurance of lot-to-lot consistency. Further, the specification for -content (the ——— is greater than or equal to — allowing up to — difference in the level of ——— The manufacturing history in fact reflects a — range. Further, significant amaounts of the : ——— are misfolded, but lot-to-lot variation has not been investigated, and no appropriate specifications have been set. Since this is a toxic molecule, and the dose is determined by protein concentration, not biological activity, this represents a significant safety concern. Finally, Seragen will be informed that no other indications will be approved with the present product.

Licensure by CBER of such an impure protein produced by recombinant DNA technology would be unprecedented. Seragen has demonstrated the ability to further purify this product using several different methods (——————— for example). We recommend that $DAB_{389}IL-2$ be further purified-prior to licensure or that a Phase IV commitment to further purify the product be adopted. If licensure of the current product is to occur, additional tests and specifications will need to be incorporated into the current lot release and stability protocols in order to assure lot-to-lot consistency. The specifications do not give assurance of the delivered dose. This represents a significant safety concern for this toxic molecule.

I. Introduction.

Seragen has submitted a BLA to market ONTAK™ (USAN name: denileukin diftitox injection) for use in patients with cutaneous T-cell lymphoma (CTCL) which is persistent or recurrent despite prior therapy. DAB,,-IL-2 was the name of the product during clinical investigation and is the name used throughout the application and in this review. $DAB_{389}IL-2$ has been granted orphan drug status. Seragen, Inc. requested accelerated approval of $DAB_{389}IL-2$ for the treatment of CTCL under 21CFR 601 Subpart E and 3 14.5 10. Seragen has been granted a priority six month review clock.

DAB_{389}-IL-2 is a fusion protein specifically designed to direct. the cytocidal action of diphtheria toxin to those eukaryotic cells bearing the IL-2R. Recombinant DNA techniques have been used to construct a fusion gene consisting of nucleotide sequences for the enzymatically active and membrane translocation domains of diphtheria toxin linked to those for human IL-2. This gene, as expressed in *E. coli*, should result in the production of a - ——— I with a molecular weight of 58 kD. DAB_{389}IL-2 is purified from ——— by reverse-phase chromatography, ———, followed by ———, and a multistep diafiltration process. DAB_{389}IL-2 is supplied as a sterile frozen solution (1 50µg/mL) in a citrate-EDTA buffer at neutral pH.

II. Drug Substance.

1. Description, DAB_{389}-IL-2 is a fusion proteinconsisting of the first 387 (Volume 2, pg. 57) amino acids of diphtheria toxin linked through a ——— with ——— to human IL-2 [(Met_1-Thr_{387})-His-Interleukin-2 (Ala,-Thr,,,)]. The USAN name is denileukin diftitox. DAB_{389}IL-2 is an interleukin-2 receptor-specific cytotoxin produced with recombinant DNA techniques by expression of a fusion gene in *E. coli*.

2. Characterization/proof of structure.

From the CMC Guidance document: "A description and the results of all the analytical testing performed on the manufacturer's reference standard lot and qualifying lots to characterize the Drug Substance should be included. Information from specific tests regarding identity, purity, stability, and consistency of manufacture of the Drug Substance should be provided."

The characterization efforts concentrated on Lot ——— the current reference material. Table 4.2-2 (attached) gives a summary of the methods and the source of the DAB_{389}IL-2 used for characterization.

Confirmation of the Primary Structure

Mass Spectral Analysis (4.2.2.1.1, Vol. 3., pg. 15)

The molecular mass of the protein was determined by ——— DAB_{389}IL-2 Purified Drug Substance which had been further purified by ——— chromatography (method similar to that described in Section 4.2.2.5.1) was used in this analvsis. Samples from two separate purification batches, ———,and' ———}) were analyzed, the main component corresponded to the predicted molecular weight. Another component consistent — DAB_{389}-IL-2 was also detected. Other heterogeneities were also found which were not characterized.

Conclusion: The CMC guidance document for specified products states that characterization tests should be done on the Drug Substance or Final Drug Product. Since this test was done on further purified product, it is not really a characterization of the Drug Substance. This test shows that the main component of the further purified Drug Substance was of the predicted molecular weight of DAB_{389}IL-2.

———. (4.2.2.1.2, Volume 3, page 17). Seragen report 96093 (provided).

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A better test for proper would be to test the of the IL-2 domain by determining IL-2 receptor binding constant and to determine the ADP-ribosylation kinetics to monitor proper of the diphtheria domain.

ACTION: We recommend that a IL-2 receptor binding assay and a ADP-ribosylation assay be used to further characterize this product. This will give assurance of proper of the molecule. If the current product is licensed, we recommend that Seragen develops an IL-2 receptor binding assay as an additional lot release test.

4.2.2.3.1
(Reduced). (Vol. 3, page 34).

A visual conformation of purity and relative percent concentration of $DAB_{389}IL$-2 is routinely determined by using the high sensitivity staining method (Section 4.6.8). doesn't provide estimation of purity. Section 4.6.8 (Vol. 6, page 196) contains a description of the assay, the assay validation is in Seragen reports 97013 and 97035 (not included in this submission).

A statement is made: "Analysis of purified drug substance yields a of the appropriate molecular weight. Refer to Section 4.2.8.2 for an example of a representative analysis." Volume 5, page 80 contains an example.

ACTION: are used to characterize the purity of this substance. We have the following comment/questions regarding this test:

a. Accurate analysis of protein purity by requires careful attention to several issues, including sample loading (mass), validation of dynamic range, choice and validation of staining methods, instrumentation used in procedures used to establish appropriate background during and subsequent data manipulations, etc.. It is widely recognized that serious errors can be introduced in purity assessments if such precautions are not taken. The use of' procedure suggests some cognizance of these issues. Nevertheless, complete information regarding these procedures should be submitted (See CMC guidance, section A2, final paragraph, and Dr.

b. A representative is found on p. 80, volume 5. This appears to have been stained with (or there was a problem with the color photograpy). The also appears to be overdestained. The molecular weight standards are not identified and the are very blurred. No information is provided regarding sample loading, detection limit, or dynamic range of the assay. No details are provided for staining and destaining procedures (there are many variants of based procedures, and ---- has published both an original and a modified procedure; several commercial kits based on both approaches are also available). The basis for the numerical estimates of product purity that are made is therefore completely unclear. The same comments apply to other data, including All analyses need to be validated to address these concerns, and the data supporting these validations submitted. It is likely that many, if not all, analyses contained in the application will need to be repeated and the data submitted.

4.2.2.3.2 (Vol. 3, page 34)

ACTION: Complete documentation of this assay should be provided including a complete description of the antibody production. This test should be further developed to be more quantitative. Immunoblots should be run with a dilution series of known protein concentration. Reduced and non-reduced SDS-PAGE gels should be used for the With adequate validation, semi-quantitative statements about concentration could be made with this test which could support data obtained by other analyses.

Question: A representative is shown in Section 4.2.8.6, Volume 5, pg. 84. This shows that although there is a major of $DAB_{389}IL\text{-}2$, there are also

forms of the product. Please explain. The also shows a hint of contaminating in the assay reference. What is the assay reference material for this

, Analysis (Vol. 3, pg. 35)

Pictures of reduced and nonreduced -gels showing Final Drug lots were provided. Both showed a ----- rand . All lots looked consistent by this method, but this is-difficult to tell without details of assay validation. analyses was used to assess product comparability during process optimization and is no longer used.

Comments: The data included in this submission indicate high levels of several impurities. Since $DAB_{389}IL\text{-}2$ is expressed in *E. coli*, the impurities are likely to result from inadequate removal of host cell proteins, inappropriate initiation or termination of translation, or protein modifications (e.g., deamidation, oxidation). Appropriate efforts to remove these impurities or explore their impact on product performance have not been made.

Amino Acid Analysis (4.2.2.3.4, Vol. 3, page 38).

The complete amino acid analysis of the protein reference standard, Final Drug Product lot 5D07HA2 is provided. Amino acid analysis was performed, under contract, by The experimental composition of $DAB_{389}IL\text{-}2$ agreed with the known composition within the expected experimental error. Amino acid analysis on a protein of this size is not informative, except as a measure of protein mass.

ACTION: The results of this assay on the reference lot are not shown. Was the reference lot assayed by this method? Since the form is more active than the form of $DAB_{389}IL\text{-}2$, this test should be used as a lot release test for Drug Substance and a specification should be set.

(4.2.2.3.6, Voi. 3, pg. 43)

Table 4.2-2, pg. 14, shows that this test was performed only on the reference lot. This very important test should be developed to assay product consistency.

ACTION: This test, or some version of it should be developed as a product consistency and release test. The tests currently used for lot release do not measure [redacted] or modified protein. This test addresses these issues. A complete description of this test, including validation, and representative data should be provided.

[redacted] (4.2.2.3.7, Vol. 3, pg. 44)

[redacted]

ACTION: A complete description and validation of this test should be provided. The amount of [redacted] from this method should be compared with that obtained by other methods such as-non-reducing SDS-PAGE gels.

Summary: The CMC guidance document states that the company should include assays to detect product-related proteins including deamidated, oxidized, cleaved, and aggregated forms. Seragen has not provided accurate documentation for this. The [redacted] could be developed to detect protein modifications. Validation of the [redacted] should include experiments to establish the assay's ability to detect [redacted] or [redacted] Tests which accurately measure [redacted] and [redacted] Drug Substance need to be developed as lot release and stability tests.

Assays to detect residual host proteins, DNA, or other reagents are included in other sections.

Clearance studies begin in Vol. 5, pg. 62 and are summarized below.

b. Biological Activity

[redacted]

Conclusion: This assay measures inhibition of protein synthesis by DAB_{389}IL-2. However, it is far too imprecise to give any indication of dosing.

QUESTIONS: What class of IL-2 receptors do C9 1/PL cells express? What is the EC,, or LC,, (if there is one) of DAB_{389}IL-2 on a cell line that does not express the IL-2 receptor?

Characterization of the Active Comuonent (Vol. 3. pp. 48)

Since, unlike specified biologics, DAB&CL-:! has not been extensively purified, Seragen has provided a section characterizing the active species in their product, in contravention to

official FDA guidance. The "specified" designation remains discretionary and the present product does not meet the requirements for this designation.

QUESTION: What was the starting material for this experiment?

4.2.2.5.2 Functional properties of _____ DAB389&-2. These studies are described in Section 5.0, Nonclinical Pharmacology and Toxicology and thus are not covered in this review

_____ A comparison of the two methods with appropriate validations should be made.

Questions: Regarding Table 4.2.11. What is the starting material for this experiment? What was the SDS-PAGE method used to estimate the _____ concentration? What percentage of the total protein applied to _____ is recovered? If less than 100%, how can reliable inferences regarding _____ content be made?

Biological Characterization of _____ and _____ 4.2.2.6.3, Vol. 3, pg. 57)

B. Manufacturer (Section 4.2.3, Vol. 3, pg. 58)

The manufacturer of Purified Drug Substance for all clinical studies and for initial commercial distribution is Seragen, Inc., 97 South Street, Hopkinton, MA. Seragen has entered into an agreement with Boston University, and Seragen's manufacturing operation will be incorporated as Marathon Biopharmaceuticals, Inc. Responsibility for manufacture of DAB&L-2 will transition to Marathon Biopharmaceuticals under contractual agreement with Seragen, Inc. Seragen, by corporate policy, will maintain functional control of all contract manufacturing. A floor diagram has been provided. A brief description of other products manufactured in the facility has been provided. A general description of the contamination precautions has been provided for equipment used in fermentation and in purification.

The review of the manufacturer will not be complete until after the inspection.

C. Method(s) of manufacture

1. Raw Materials and Reagents.

A list of raw materials has been provided, however no certificates of analysis from the suppliers and/or manufacturer's acceptance criteria have been included.

Action: As stated in CMC guidance, p.6 "Representative certificates of analysis from the supplier(s) and/or manufacturer's acceptance criteria should be included in this submission. Process gases (e.g., air, carbon dioxide) and water are considered raw materials."

2. Flow charts

From the CMC guidance document, page 7: "A complete visual representation of the manufacturing process flow should be provided. This flow chart should indicate the step in production, the equipment and materials used, the room or area where the operation is performed and a complete list of in-process controls and tests performed on the product at each step..."

No such flow chart has been included in this submission (that I could find). Section 4.2.4.2, Vol. 3, page 102 is titled "Flow Charts and Overview", but no visual flow chart is provided. A written description is provided, however, a visual flow chart would be very useful for me to have to take on inspection.

Attached are the "flow charts" that Seragen has provided. Table 4.2-24, (Vol. 3, pg. 106) Fermentation and [redacted] Table 4.2-25 (Vol. 3, pg. 106), Fermentation and Primary Recovery [redacted], Table 4.2-26 (Vol. 3, pg. 107), Purification Process Flow, Table 4.2-27 (vol. 3, 108), [redacted] process testing, Table 4.2-27 (Vol. 3, pg. 109).

3. Detailed description

a. Animal Sources (Vol. 3., pg. 112).

Only [redacted] are derived from an animal source. It is stated that [redacted] are derived from [redacted] or [redacted] source herds which are free of Bovine Spongiform Encephalopathy.

No Certificates of Analysis have been submitted.

Action: Submit a representative certificate of analysis for ------

b. Cellular Sources

DAB_{389}IL-2 protein is produced in *E. coli* strain

I. Host Cells

II. Gene Construct

ii. Cell Seed lot system

A. Master cell bank (vol. 3, pg. 118) and B. Working Cell Bank (Vol. 3, pg. 118)

A general description of the preparation of the MCB was provided.

A general description of the preparation of the WCB was provided.

The tests on the MCB and WCB are in Tables 4.2-30 and 4.2-31 (attached).

Action: The media used to grow the master and working cell banks should be described. No tests for contamination with either **lytic** or lysogenic bacteriophages or non-host microorganism(s) were included. As stated in the CMC guidance, (pg. 10, section C.3.B.V) the results of such tests should be submitted.

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A specification for [redacted] present in the polysorbate 20 is discussed below.

4. BATCH RECORDS

An unexecuted batch record was provided. A completed (executed) representative batch record of the process of production of the drug substance should be submitted.

Action: Please submit an executed batch record for a Drug Substance qualification lot.

Question: Vol. 4, pg. 235. What do [redacted] and [redacted] stand for?

D. Process Controls (Section 4.2.6, beginning on pg. 1, Volume 5).

Table 4.2-48 (Vol. 5, pg. 1, attached) describes the in-process controls for fermentation and primary recovery of DAB,,&-2. The specifications are not presented on this table.

[redacted]

[redacted]

Action: As stated above, a complete description of the [redacted] system should be provided. It should include information on the validation of [redacted] and information [redacted]. [redacted] are used to assess the product purity at many different steps in the purification. Is the same SOP used for all [redacted]

4.2.6.3.4 [redacted], Assay (Vol. 5, pg. 17)

Action: What is meant by "conform to reference?" As stated above, documentation of validation of this test should be provided.

Purification and Activation In-Process testing (Vol. 5, pg. 19).

Table 4.2-50 (attached) describes the purification and In-process testing, but does not give the specifications. Some of the tests shown in step [redacted] should be developed as lot release tests for the Drug Substance.

Action: We recommend that the [redacted] be developed and validated as a lot release test. The [redacted] should also be included as a lot release test.

The [redacted] [Vol. 5, pg. 20) is used to determine the protein concentration of material to be. purified by Reverse-Phase [redacted] Chromatography (Section 4.6.2).

4.2.6.5.2.2, Vol. 5, **pg. 20.**

Action: This specification should be tightened up. This is the only purification step in the entire procedure. This specification should be set at

4.2.6.5.3.1 Reverse-Phase Chromatographic Assay (Section **4.6.22)** is used to of the DAB$_{390}$IL-2 protein.

Action: A complete description of this assay should be provided This is the only indication of the amount of properly we have. Table 4.2-52 (Vol. 5, pg. 26-27) shows a range in This assay indicates that the amount of properly in the final product.

Please explain Figure 4.2-27 in detail. What makes up ? How was this determined?

4.2.6.7 Validation studies for the cell growth and harvesting process.

4.2.7.3.1 , (Vol. 3, pg. 38).

data were submitted. The details of this protocol are described in Seragen Report 9607 1.

Action: Please submit Seragen report 9607 1.

4.2.6.8 Validation studies for the purification process (Vol. 5., pg. 40)

Multi-variable protocols were used to evaluate different parameters for reverse-phase chromatography conditions, diafiltration and conditions and reverse-phase preparation procedures. The sponsor states that none-of the conditions varied impacted the product. However, very little data was provided and this was difficult to evaluate.

This must be a misprint since most of the samples did not meet this criterion and but passed this test (page. 53).

Question: On Vol. 5, page 52 it is stated that the acceptance criterion for purity was greater than or equal to yet most of the runs did not meet this criteria (Table 4.2-75, Vol. 5, pg. 53). Please explain.

4.2.6.8.3.3 Reverse-Phase Chromatoeranhv (Vol. 3. no. 54)

Question: Vol. 5, pg. 55. It would have also been appropriate to test for protein modification such as and 'lease comment. What is the hold temperature range used?

4.2.6.8.3.4 Concentration (Vol 5 no 55)

Question: Why is this specification so broad? Since is a critical manufacturing process, this should be better controlled. Assays to validate the concentration of used should measure forms of DAB,,&-2. gels and would be appropriate. Sponsor could do validation studies showing that a -- range in levels has no effect on the percentage of active . --- and other impurities.

Comment: Vol. 5, pg. 57. The mixing conditions for the purified drug substance were validated using — and — polysorbate 20 more appropriate test for mixing would have been albumin (or another protein) and polysorbate 20. Please comment.

Other things tested were: shipping conditions, non-specific protein binding to ——. —— filters, onerational speeds during diafiltration, —— of the --- ——— None of the variables tested affected the purified drug substance. However, tests for --- or modified protein were not included.

4.2.6.9 Clearance Studies (Vol. 5, pg. 62).

No clearance studies for — Neomycin or ——— were performed. Calculations provided show that if these components partition equally into the —— and the — the amounts would be very small prior to purification.

——— and ——— were summarized. However, the summarized versions were hard to understand.

Action: Please submit the Seragen reports which describe the removal of ———

Endotoxin removal is validated by repeated testing throughout the manufacturing and in the final drug substance. This is valid.

No other clearance studies were provided.

C. Microbiology

From the CMC guidance document: A description and validation studies for any processes used for media sterilization, inactivating cells prior to their release to the environment, if such inactivation is required, etc., should be provided. If the Drug Substance is intended to be sterile, information should be submitted as described in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

——— No documentation was provided. A Seragen report was referenced.

E. Reference Standard

Action: A summary of the data obtained on the reference lot ——— was provided (Table 4.2-84, Vol. 5, pg. 72). All original data regarding the reference lot should be provided. As requested in the CMC guidance document, the SOP for the selection, evaluation and release of the Assay Reference lot should be provided.

4.2.7.2.1 Protein Reference Standard (Vol. 5, pg. 73)

This standard is used for quantitation of $DAB_{389}IL\text{-}2$ by reduced - - -

Question: Is this same standard used for non-reduced ———

4.2.7.2.2 DNA Reference Standard (Vol. 5, pg. 74).

The description of the DNA reference standard is adequate.

Comment: Validation of DNA removal during the purification process would be an option for a further purified product.

4.2.7.2.3 Bioassay Reference Standard

This reference material is used to generate the standard response curve for determining $DAB_{389}IL\text{-}2$ bioactivity. The current bioassay reference standard is [redacted]

Action: Please submit the SOPs for preparation, storage and evaluation of standard.

F. Specifications/Analytical Methods

General comment: The descriptions of the tests in this section are not complete enough to judge their suitability for lot release tests. A complete description of each test and the validations of the tests should have been provided in this section. We will request the details of what we consider to be the most important tests.

4.2.8.1 [redacted]
(Vol. 5, pg. 78). This is used to determine protein concentration.

Question: How was this assay validated? It would be appropriate to validate this assay against a reference method (e.g., nitrogen determination, quantitative amino acid analysis, etc.). An important part of this validation will be mass balance studies to evaluate recovery of total protein from the [redacted] The possibility of [redacted] has not been addressed.

Question: Is Figure 4.2-29 (Vol. 5., pg. 78) the result of reduced or non-reduced [redacted]

4.2.8.3 DNA Assay (Vol. 5 5, pg. 81)

A [redacted] DNA assay is used for the determination of residual chromosomal E. coli DNA in Purified Drug Substance.

Comment: An efficient, robust purification scheme (e.g., with an ion-exchange step) , would allow this to be dealt with via a validation/challenge study at lab scale.

4.2.8.4 Polysorbate 20 Assay

[redacted] is used to quantitate the Polysorbate 20 concentration in the Purified Drug Substance.

Question: Are there any pharm/tox issues for polysorbate 20?

4.2.8.5 [redacted] for determination of [redacted] and [redacted] in the Purified Drug Substance.

Question: How was this assay validated? Please submit a complete description of this assay with assay validation data.

4.2.8.6 [redacted] assay (Vol. 5, pg. 83).

The description of the [redacted] assay is inadequate. From the description it seems that they just look at the [redacted] and compare it to the reference.

Question: [redacted] assay (Vol. 5, pg. 83) What is the "Assay Reference"? Is the "assay reference" a characterized (e.g., homogenous, sequenced) standard run as a control? Both the signal intensity and molecular weight should be within specified limits. Dilution series of a standard would be appropriate. With appropriate controls, this assay will also provide useful information regarding product-related impurities.

Question: Fig. 4.2-33., Vol. 5, pg. 85. It looks as if the reference standard may be contaminated with *E. coli* protein. Please comment.

4.2.8.7 [redacted] (Vol. 5, pg. 85).

The sponsor has submitted a [redacted] that has both reduced and non-reduced DAB,,&-2. (Fig. 4.2-34, Vol. 5, pg. 85). the non-reducing [redacted] data suggest much higher levels of ----- than of the [redacted] profiles. Might substantial amounts of [redacted] material be hanging up on the [redacted] Non-reducing [redacted] before and after [redacted] (identical amounts of protein) might resolve this.

4.2.8.8 [redacted] (Vol. 5, pg. 86).

Comments: As stated above, this test is currently an "in-process" test, it should be changed to a lot release test. If properly validated, this test will be very helpful for lot to lot comparability. The ---- , could be made quantitative by [redacted] and; [redacted] to a [redacted]

4.2.9 Purified Drug Substance Batch Specifications/Results

This section lists all released batches, all stability batches and all currently quarantined batches (pg. 91-106). Early bathes had a long list of release tests (pg. 93), while current release specifications are minimal (Table 4.2-88, pg. 107, attached).

The company states that the identity test is the [redacted] This is not sufficient; we recommend that a [redacted] and/or a [redacted] be included in the lot, release tests.

Seragen has one test called [redacted] This is a [redacted] , It is misleading to call this [redacted] The company should change this name to [redacted]

We generally request two purity tests with non-correlated molecular selectivities. In this case, we will request that [redacted] be developed as a purity test to be used in addition to [redacted]

There is no test for the amount of---- and [redacted] -DAB_{389}IL-2 in there release specifications. Since [redacted] DAB_{389}IL-2 is more active than the [redacted] -form, a specification should be set for this.

Action: Regarding the specifications for lot release for Drug Substance:

Action: Certificates of analysis for the qualification lots were not included. pg. 16, Guidance for industry document explicitly states that certificates of analysis and analytical results for at least three consecutive qualification lots of the drug substance should be submitted.

2. Impurities profile (Vol. 5, pg. 109)

A description of how the --- was characterized should be submitted. (Seragen report 95 130).

Product-related Impurities (Vol. 5, pg. 113)

Action: of $DAB_{389}IL-2$ can t (Vol. 5, pg. 113). We recommend that this system, or a related system be developed as a purification step for the drug substance. An extensive study of the has been provided. We request the following additional information:

On Vol. 5, pg. 116, it is stated that ; are not biologically active. Seragen report 94122 is referenced. This should be submitted.

The -- was characterized via Vol. 5, pg. 123 gives the results of this study. The study suggested that the- is ------ A in the ----- however, were not detected, so the characterization study is incomplete.

Summary: For designation as a specified biologic, much more careful analysis of the impurities profile or elimination of most impurities will be required.

4.2.10.3.2.3 Reverse-Phase [redacted] Chromatography [redacted]

[redacted]

[redacted]

Action: Vol. 5, pg. 125 states that the main active [redacted] is [redacted] This is not acceptable for a specified product. At the very least, this test should be run as a release test and specifications should be set so that the amount of [redacted] varies by no more than [redacted]

[redacted]

[redacted]

The level of this impurity was not assessed. An alternative method to [redacted] should have been used to address the level of this impurity. Please comment.

Regarding the [redacted] shown on Vol. 5, pg. 162. These lots of final product do not look very pure by this analysis.

4.2.12 Drug Stability program (Vol. 5, pg. 175).

[redacted]

[redacted]

4.2.12.3 [redacted] (discussed in detail in Section 4.3.8.5.2.2)

4.2.12.2.2. Stability at [redacted] 'Vol. 5, pg. 177)

[redacted]

Action: The stability studies are insufficient. The current stability protocol does not adequately address the percent [redacted] or the percent. [redacted]

Expiration Dating Analysis

(Volume 2, page 8 1) Expiration dating analysis has been performed on bioactivity and [redacted]

indicated that the expiration dating period for $DAB_{389}IL-2$ Final Drug Product, stored at nominal - 10°C, could be set conservatively at 12 months.

A strategy for storage and release of the Final Drug Product has been developed based upon this data. All inventory may be stored at -80°C for up to [redacted] All vials will be labeled at the time of fill (as validated). At the time of Final Drug Product fill, [redacted]

4.3 Drug Product, Vol. 6, pg. 1.

The composition of the Drug Product is shown in Table 4.3-1, Vol. 6, pg. 1. The excipients are listed and tests are referred to.

4.3.3 (Vol. 6, pg. 2) The manufacturers are listed. A list of responsibilities has been submitted. A list of all other products made in the same rooms has been provided.

4.3.4 Methods of Manufacture and Packaging

Everything that is requested in the guidance for industry document seems to be included. A review of this section will not be complete until it undergoes a pre-license inspection.

Question: Vol. 6, pg. 32, Representative Batch History- Lot - This filling took over two times as long as the other representative batches, please explain.

Specifications and test methods for Drug Product.

Vol. 6, pg. 34. The sampling procedure is clearly defined and adequate.

4.3.5.2 Specifications and Methods (Vol. 6, pg. 35).

Action: A complete description of all lot release test, including validation methods and data should be submitted.

Question: Regarding the . shown in Vol. 6, pg. 42. Can the percent be quantitated using this assay? How does this compare with the percent -- found with the assay?

Vol. 6, pg. 53 lists the Final Drug Product Specifications (attached).

Action: Certificates of Analysis and analytical results for at least three consecutive batches of Final Drug Product should be provided.

4.3.6 Container Closure System (Vol. 6, pg. 54) The information provided in this section is adequate.

4.3.7 Microbiology (Vol. 6, pg. 60).

This section will be reviewed in detail during the prelicense inspection.

4.3.8 Drug Product Stability (Vol. 6, pg. 114).

4.3.8.3 Test Methods

The stability-indicating capability of the various test methods used to characterized $DAB_{389}IL-2$ were evaluated using samples of $DAB_{389}IL-$ Final Drug Product.

The stability indicating tests were:

1.
2.

As indicated above, a test for should have been included.

The three lots used for stability studies had relatively low [redacted] concentrations [redacted]). At -26°C and -80°C, no decrease in this concentration was observed up to [redacted]

The expiration dating was set at 12 months for - 10°C.

Stability at 25°C shows a steady decline ir [redacted] over a [redacted] period. Storage at this temperature is not recommended.

4.3.8.2.2.3 Stability at 40°C

[redacted]

4.3.8.2.6 Effect of light on stability (Vol. 6, pg. 137).

[redacted]

4.4 lnvestigational Product/Formulation (Vol. 6, pg. 140).

The initial clinical formulation was a [redacted] buffer. The current formulation, a citrate buffer, was used in the pivotal clinical trials.

[redacted]

4.4.2.3 Purification Process Evolution (Vol. 6, pg. 164).

4.5 Environmental Assessment

Seragen has requested a categorical exclusion to the provision for submission of an Environmental Assessment in accordance with 21 CFR 25.3(a) and 25.3 (b).

4.6 Methods Validation

The information on the methods was minimal. We will ask them to send complete reports

This test was discussed above.

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